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Increased serum alkaline phosphatase activity in ankylosing spondylitis

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SUMMARY Raised serum alkaline phosphatase (AP) levels were found in 13 of 76 patients (17%) with ankylosing spondylitis (AS), and 11 of these 13 underwent further investigation to determine the origin of the increased enzyme activity. Three had levels within the normal reference range on re-estimation, and, of the remaining 8, AP isoenzyme studies indicated an increased liver fraction in 6. Serum gamma-glutamyl transpeptidase (GGT) was raised in only 3 patients. Increased AP activity did not appear to be directly related to disease activity or to drug therapy. These findings confirm the occurrence of increased serum AP activity in AS but challenge a previously reported suggestion that bone is the source of the increased enzyme.

The serum level of alkaline phosphatase (AP) may rise in a variety of inflammatory rheumatic diseases.[1,2] The source of the increased enzyme activity is usually the liver,[1-4] but it has been suggested that it arises from bone in ankylosing spondylitis (AS).[5] We have investigated the prevalence of raised AP in AS and attempted to determine the origin of the increased enzyme activity by isoenzyme studies and by reference to other liver enzymes, specifically alanine transaminase (ALT) and gamma-glutamyl transpeptidase (GGT).

Patients and methods

Sixty-seven men and 9 women, aged 18–71 years, with AS as defined by the New York criteria, were assessed clinically, haematologically, and biochemically. Five had associated psoriasis, 2 Reiter's disease, and 4 chronic inflammatory bowel disease. The mean duration of spondylitic symptoms was 14·9 years.

The initial laboratory investigations included haemoglobin, full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and a serum biochemical screen for calcium, phosphate, AP, total protein, albumin, bilirubin, and ALT. Repeats of these tests with additional AP isoenzyme studies and estimation of GGT were performed on patients found to have AP levels above 13 King-Armstrong units (KAU)/dl, the upper limit of the normal reference range.

All blood samples were collected between 9 am and 1 pm.

The ESR was measured by the Westergren method and CRP by Mancini radial immunodiffusion on Hoechst plates. The biochemical screen was performed with a Vickers M300 Analyser.

AP isoenzyme separations were performed by electrophoresis on agarose (Corning Medical, California), bands of activity being identified by areas of fluorescence appearing after hydrolysis of naphthyl AS-MX phosphate. The serum was electrophoresed with and without prior heat inactivation at 56°C for 10 minutes to identify the heat labile bone isoenzyme and compared with samples containing bone or liver isoenzyme. Differential heat stability was also determined by the method of Moss and Whitby.[6]

Serum GGT activity was measured at 25°C by reaction rate with a Boehringer kit (Boehringer Mannheim GmbH).

Results

Thirteen patients (17%) had AP levels above the upper limit of the reference range, and 11 (see Table 1) returned for further investigation. Eight other patients had borderline values of 13 KAU/dl and were not retested. Of the 11, 3 had a normal AP on the second occasion. In the other 8 the isoenzyme studies indicated an increased liver fraction in 6, an

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Table 1 *Details of 11 patients with ankylosing spondylitis and increased serum alkaline phosphatase activity who underwent*

Case	*Age*	*Sex*	*Clinical activity*	*Associated conditions*	*Drugs*	*ESR (mm/h) (<15)*	*CRP (mg/l) (<10)*
1	27	M	Inactive	(Pulmonary tuberculosis)	Rifampicin Isoniazid	4	11
2	35	M	Active	—	—	5	9
3	43	F	Inactive	—	—	21	7
4	43	M	Active	Psoriasis	Indomethacin Amiloride/ Hydrochlorothiazide	3	9
5	38	M	Active	—	Indomethacin Piroxicam Pentazocine/ Paracetamol	21	14
6	27	M	Active	—	—	13	20
7	43	M	Inactive	Reiter's disease	—	75	71
8	33	M	Active	—	—	54	25
9	49	M	Active	—	Indomethacin Piroxicam	52	23
10	36	F	Inactive	Ulcerative colitis Sclerosing cholangitis	Sulphasalazine	25	8
11	64	M	Active	Peripheral arthritis	Prednisolone Phenylbutazone	3	8

increased bone fraction in one, and a normal pattern in one. A raised GGT was seen in 3 patients, being associated with a predominantly liver isoenzyme pattern in 2 and a normal AP in the other. ALT was within normal limits in all patients. The highest AP and GGT levels occurred in a patient with associated ulcerative colitis and sclerosing cholangitis (no. 10 in Table 1), while the patient with the increased bone fraction of AP (no. 11) had predominant limb joint symptoms. Increased liver AP activity was associated in 5 of the 6 cases with a raised CRP, and 4 of these had clinically active disease. Of the 2 cases with an elevated liver enzyme fraction who appeared inactive clinically one (no. 10) was the patient with ulcerative colitis and sclerosing cholangitis, who had a normal CRP, and the other (no. 7) had Reiter's disease and the highest CRP of the series. The 4 patients with a normal isoenzyme pattern had a normal, or in one case a marginally elevated, CRP and clinically inactive spondylitis. The ESR also was raised in 5 of the 6 patients with increased liver enzyme activity and was normal in all but one of the remainder.

Discussion

Despite its well known nonarticular features, AS, unlike rheumatoid arthritis, is not generally regarded as a systemic disease, and the increase in AP activity that sometimes occurs is not widely recognised. A recent review of the association between arthritis and liver disease in fact failed to mention AS as a cause of disturbance of liver function.[7] Our finding of increased AP activity in 17% of patients with AS compares with figures of 47·5%[5] and 13%[8] reported in other series. Kendall *et al.*[5] attributed rises to increased bone production, but our isoenzyme studies suggest that the increase is mainly of liver origin. The finding of a normal GGT in several of these patients came as a surprise, as GGT is usually regarded as a more sensitive indicator than AP of liver disease, including cholestasis.[9] However, a similar discrepancy between GGT and AP levels has been reported in rheumatoid arthritis by Spooner *et al.*,[10] who found concurrent elevations of both enzymes in only 12 of 98 patients, of whom 23 had increased GGT and 45 increased AP activity.

Although AP levels did not appear to be related to clinical disease activity, ESR, or CRP in the 76 patients as a whole, it is notable that where elevated AP levels were found to be due to increased liver AP activity all 6 cases had a raised ESR or CRP or both, and 4 of them had clinical evidence of activity. By contrast, the 4 patients with normal isoenzyme patterns (including the 3 who had normal AP values on

further investigation

AP (KAU/dl) (3–13)		*AP isoenzyme distribution*	*ALT (U/l) (<20)*	*γGT (U/l) (M<28 F<18)*	*Calcium (mmol/l) (2·19–2·50)*	*Phosphate (mmol/l) (0·6–1·3)*	*Total protein (g/l) (61–77)*	*Albumin (g/l) (41–51)*	*Bilirubin (μmol/l) (<19)*
Initial	*Repeat*								
14	11	Normal	7	17	2·41	0·8	77	44	5
15	12	Normal	6	8	2·39	0·8	71	45	11
16	12	Normal	11	19	2·38	1·1	71	42	6
19	14	Normal	6	16	2·76	0·9	77	50	6
14	14	Predominantly liver	12	15	2·41	0·6	75	45	5
15	14	Predominantly liver	1	13	2·48	1·0	73	44	—
17	16	Predominantly liver	2	20	2·44	0·8	86	42	4
18	18	Predominantly liver	9	18	2·25	0·7	76	34	3
24	19	Predominantly liver	13	32	2·42	1·0	77	41	6
17	20	Predominantly liver	11	94	2·50	1·1	74	43	15
15	16	Predominantly bone	6	26	2·32	0·9	70	42	6

retesting) had normal or only slightly raised ESRs and CRPs and clinically inactive disease. Thus, there is some evidence that the AP disturbance might be related to disease activity in AS as previously reported.[5]

Several nonsteroidal anti-inflammatory drugs are known to be potentially hepatotoxic, with reports of liver damage ranging from transitory mild disturbances of liver function tests to fatal hepatitis and intrahepatic cholestasis,[11 12] but drug therapy did not appear to be implicated in the disturbance of AP activity in our patients. Four of these with elevated levels were not receiving anti-inflammatory medication, and the 3 whose values were normal on rescreening were on no medication at the time when their AP levels were raised.

The significance of increased AP activity in AS remains obscure, but it may simply be a nonspecific reaction to the inflammatory process. It would appear that small increases do not warrant further investigation, but, when high levels are found in apparently uncomplicated spondylitis, primary hepatic disease and drug toxicity should be excluded.

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